

What is claimed is:

1. A method of detecting ligand binding to a heterologous G protein coupled receptor comprising:
 - a) providing transformed yeast cells comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, each said gene being under the control of a separate promoter, and a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of: sst2, STE50, sgvl, ste2, ste3, pik1 afr1, msg5, and sig1;
 - b) combining said cells with a compound to be tested; and
 - c) detecting if said compound binds to said heterologous G protein coupled receptor.
2. The method of claim 1, wherein said heterologous G protein coupled receptor is a mammalian G protein coupled receptor.
3. The method of claims 1 or 2, wherein said transformed yeast cells further comprise a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.
4. The method of claim 3, wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of sst2, STE50, sgvl, ste2, ste3, pik1 and afr1.
5. The method of claim 3, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a FAR1 or FUS3 gene.
6. The method of claims 1 or 2, wherein the reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1, Lacz and CYH2, and the pheromone-responsive promoter is FUS1.

7. The method of claim 6, wherein said transformed yeast cell further comprises a mutation at a FAR1 or FUS3 gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.
8. The method of claim 7, wherein said reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1, and Lacz.
9. The method of claim 6, wherein said transformed yeast cell further comprises a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.
10. The method of claims 9, wherein said reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1, and Lacz.
11. The method of claim 6, wherein said reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1 and Lacz.
12. The method of claims 1 or 2, wherein the gene mutations causing increased sensitivity to receptor activity are sst2 and msg5.
13. The method of claims 1 or 2, wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of sst2, STE50, sgv1, ste2, ste3, pik1 and afr1.
14. The method of claim 1, wherein said heterologous G protein-coupled receptor is selected from the group consisting of .beta.2 adrenergic receptor, .alpha.2 adrenergic receptor, 5HT1-A receptor, muscarinic acetylcholine receptor, growth hormone releasing factor receptor, and somatostatin receptor.
15. The method of claim 14, wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of sst2, STE50, sgv1, ste2, ste3, pik1 and afr1.
16. A method of detecting ligand binding to a heterologous G protein coupled receptor comprising:

a) providing transformed yeast cells comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, each said gene being under the control of a separate promoter, and a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest;

b) combining said cells with a compound to be tested; and

c) detecting if said compound binds to said heterologous G protein coupled receptor.

17. The method of claim 16, wherein said heterologous G protein coupled receptor is a mammalian G protein coupled receptor.

18. The method of claims 16 or 17, wherein said yeast cells further comprise a heterologous adenylylcyclase.

19. The method of claim 18, wherein said yeast cells further comprise a mutation of the *cdc35* gene.

20. The method of claim 19, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a *FAR1* or *FUS3* gene.

21. The method of claim 1, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a *FAR1* or *FUS3* gene.

22. The method of claims 16 or 17, wherein said yeast cells further comprise a heterologous PLC.sub.b.

23. The method of claim 22, wherein said yeast cells further comprise a mutation in the *plc1* gene.

24. The method of claim 23, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a FAR1 or FUS3 gene.
25. The method of claim 22, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a FAR1 or FUS3 gene.
26. The method of claims 16 or 17, wherein said transformed yeast cell further comprises a heterologous G protein-gated potassium channel wherein said yeast cell is unable to grow on low potassium media.
27. The method of claim 26, wherein said transformed yeast cell further comprises trk1 and trk2 mutations.
28. The method of claim 27, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a FAR1 or FUS3 gene.
29. The method of claim 26, wherein said transformed yeast cell further comprises heterologous G.beta..gamma. subunits.
30. The method of claim 29, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a FAR1 or FUS3 gene.
31. The method of claim 26, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a FAR1 or FUS3 gene.
32. The method of claims 16 or 17, wherein the reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1, Lacz and CYH2, and the pheromone-responsive promoter is FUS1.

33. The method of claim 32, wherein said transformed yeast cell further comprises a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of *sst2*, *STE50*, *sgv1*, *ste2*, *ste3*, *pik1*, *afr1*, *msg5* and *sig1*.

34. The method of claim 33, wherein the gene mutations causing increased sensitivity to receptor activity are *sst2* and *msg5*.

35. The method of claim 33, wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of *sst2*, *STE50*, *sgv1*, *ste2*, *ste3*, *pik1* and *afr1*.

36. The method of claim 33, wherein said reporter gene is selected from the group consisting of *HIS3*, *G418r*, *URA3*, *LYS2*, *CAN1*, and *Lacz*.

37. The method of claim 33, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a *FAR1* or *FUS3* gene.

38. The method of claim 32 wherein said transformed yeast cell further comprises a mutation in a *SCG1/GPA1* gene.

39. The method of claim 38, wherein said transformed yeast cell further comprises a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of *sst2*, *STE50*, *sgv1*, *ste2*, *ste3*, *pik1*, *afr1*, *msg5* and *sig1*.

40. The method of claim 39, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a *FAR1* or *FUS3* gene.

41. The method of claim 39, wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of *sst2*, *STE50*, *sgv1*, *ste2*, *ste3*, *pik1* and *afr1*.

42. The method of claim 38, wherein said reporter gene is selected from the group consisting of *HIS3*, *G418r*, *URA3*, *LYS2*, *CAN1*, and *Lacz*.

43. The method of claim 39, wherein said reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1, and Lacz.
44. The method of claim 38, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a FAR1 or FUS3 gene.
45. The method of claim 16, wherein said heterologous G protein-coupled receptor is selected from the group consisting of .beta.2 adrenergic receptor, .alpha.2 adrenergic receptor, 5HT1-A receptor, muscarinic acetylcholine receptor, growth hormone releasing factor receptor, and somatostatin receptor.
46. The method of claim 45, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a FAR1 or FUS3 gene.
47. A method of detecting ligand binding to a heterologous G protein coupled receptor comprising:
- a) providing transformed yeast cells comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, each said gene being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid G.alpha. protein;
 - b) combining said cells with a compound to be tested; and
 - c) detecting if said compound binds to said heterologous G protein coupled receptor.
48. The method of claim 47, wherein said heterologous G protein coupled receptor is a mammalian G protein coupled receptor.
49. The method of claims 47 or 48, wherein said hybrid G.alpha. protein comprises yeast G.alpha. protein sequences and heterologous G.alpha. protein sequences.

50. The method of claims 47 or 48, wherein said transformed yeast cell further comprises a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of: *sst2*, *STE50*, *sgv1*, *ste2*, *ste3*, *pik1*, *afr1*, *msg5*, and *sig1*.

51. The method of claim 50, wherein said transformed yeast cell further comprises a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

52. The method of claim 51, wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of *sst2*, *STE50*, *sgv1*, *ste2*, *ste3*, *pik1* and *afr1*.

53. The method of claim 51, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a *FAR1* or *FUS3* gene.

54. The method of claim 50, wherein the gene mutations causing increased sensitivity to receptor activity are *sst2* and *msg5*.

55. The method of claim 50 wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of *sst2*, *STE50*, *sgv1*, *ste2*, *ste3*, *pik1* and *afr1*.

56. The method of claims 47 or 48, wherein the reporter gene is selected from the group consisting of *HIS3*, *G418r*, *URA3*, *LYS2*, *CAN1*, *LacZ*, and *CYH2* and the pheromone-responsive promoter is *FUS1*.

57. The method of claim 56, wherein said reporter gene is selected from the group consisting of *HIS3*, *G418r*, *URA3*, *LYS2*, *CAN1*, and *LacZ*.

58. The method of claim 47, wherein said heterologous G protein-coupled receptor is selected from the group consisting of β_2 adrenergic receptor, α_2 adrenergic receptor, 5HT1-A receptor, muscarinic acetylcholine receptor, growth hormone releasing factor receptor, and somatostatin receptor.

59. The method of claims 1, 16, or 47, wherein said heterologous G protein-coupled receptor gene encodes a receptor selected from the group consisting of .beta.2 adrenergic receptor, .alpha.2-adrenergic receptor, 5HT-1A receptor, muscarinic acetylcholine receptor, growth hormone releasing factor receptor, somatostatin receptor, cholecystokinin receptor, and adenosine receptor.

60. The method of claim 59, wherein said heterologous G protein-coupled receptor is selected from the group consisting of .beta.2 adrenergic receptor, .alpha.2 adrenergic receptor, 5HT1-A receptor, muscarinic acetylcholine receptor, growth hormone releasing factor receptor, and somatostatin receptor.

61. The method of claims 1, 16, 47, 2, 17, or 48, wherein said transformed yeast cell further comprises a heterologous G.alpha. subunit.

62. A method of detecting ligand binding to a hybrid G protein coupled receptor comprising:

a) providing transformed yeast cells comprising a reporter gene under control of a pheromone-responsive promoter, a DNA expression vector capable of expressing the hybrid G protein coupled receptor, said receptor being capable of binding to endogenous yeast G protein, and a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest;

b) combining said cells with a compound to be tested; and

c) detecting if said compound binds to said hybrid G protein coupled receptor.

63. The method of claim 41, wherein said hybrid G protein coupled receptor comprises a sequence from a yeast G protein coupled receptor and a sequence from a mammalian G protein coupled receptor.

64. The method of claims 62 or 63, wherein said hybrid receptor comprises sequences from yeast receptors, including intracellular sequences, and sequences from heterologous receptors.

65. The method of claim 64, wherein the sequences from the yeast receptors are selected from the group consisting of STE2 or STE3.

66. The method of claims 62 or 63, wherein the reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1, Lacz, and CYH2 and the pheromone-responsive promoter is FUS1.

67. The method of claim 66, wherein said transformed yeast cell further comprises a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

68. The method of claim 66, wherein said transformed yeast cell further comprises a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of sst2, STE50, sgv1, ste2, ste3, pik1, afr1, msg5 and sig1.

69. The method of claim 68, wherein said transformed yeast cell further comprises a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

70. The method of claim 66, wherein said reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1 and Lacz.

71. The method of claims 62 or 63, wherein said transformed yeast cell further comprises a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

72. The method of claim 41, wherein said reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1, and Lacz.

73. A method of detecting ligand binding to a heterologous G protein coupled receptor comprising:

a) providing transformed yeast cells comprising a reporter gene under control of a pheromone-responsive promoter, and a heterologous C protein-coupled receptor gene, each said gene being under the control of a separate promoter, said heterologous G protein-coupled

receptor being capable of binding to endogenous yeast G.alpha. protein;

b) combining said cells with a compound to be tested; and

c) detecting if said compound binds to said heterologous G protein coupled receptor.

74. The method of claim 73, wherein said heterologous G protein coupled receptor is a mammalian G protein coupled receptor.

75. The method of claims 73 or 74 wherein said transformed yeast cells further comprise a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of: sst2, STE50, sgv1, ste2, ste3, pik1, afr1, msg5 and sig1.

76. The method of claim 75, wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of sst2, STE50, sgv1, ste2, ste3, pik1 and afr1.

77. The method of claim 75, wherein the gene mutations causing increased sensitivity to receptor activity are sst2 and msg5.

78. The method of claims 73 or 74, wherein the reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN 1, Lacz and CYH2, and the pheromone-responsive promoter is FUS1.

79. The method of claim 78, wherein said reporter gene is selected from the group consisting of HIS3, G418r, URA3, LYS2, CAN1, and Lacz.

80. The method of claim 78, wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of sst2, STE50, sgv1, ste2, ste3, pik1 and afr1.

81. The method of claims 78, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a FAR1 or FUS3 gene.

82. The method of claims 73 or 74, wherein said transformed yeast cells further comprise a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

83. The method of claim 82, wherein said gene mutation causing increased sensitivity to receptor activation is selected from the group consisting of *sst2*, *STE50*, *sgv1*, *ste2*, *ste3*, *pik1* and *afr1*.

84. The method of claim 82, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a *FAR1* or *FUS3* gene.

85. The method of claim 16 or 17, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a *FAR1* or *FUS3* gene.

86. The method of claim 32, wherein said reporter gene is selected from the group consisting of *HIS3*, *G418r*, *URA3*, *LYS2*, *CAN1* and *LacZ*.

87. The method of claim 32, wherein said mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest is chosen from the group consisting of mutations at a *FAR1* or *FUS3* gene.

88. The method of claim 61, wherein said heterologous G.alpha. subunit is selected from the group consisting of a *Gs* subunit, a *Gi* subunit, a *Go* subunit, a *Gz* subunit, a *Gq* subunit, a *G11* subunit, and a *G16* subunit.

89. A method of assaying a peptide for agonist or antagonist activity against a non-yeast receptor which comprises providing a yeast cell which expresses a heterologous G-protein coupled receptor, a G-protein capable of transducing a signal from said receptor to genes in the pheromone signal pathway of said cell, and a heterologous peptide, where, if said peptide is an agonist or antagonist for said receptor, it will stimulate or inhibit, respectively, said pheromone signal pathway, and where said stimulation or inhibition is a screenable or selectable event, which cell functionally express said receptor and said peptide, and determining whether the pheromone signal pathway is activated or inhibited by said peptide.

90. The method of claim 89 in which the cells comprise a pheromone-responsive selectable marker, and cells are selected for expression of a peptide having the desired agonist or antagonist activity.
91. The method of claim 89 in which the cells comprise a pheromone-responsive screenable marker, and cells are screened for expression of a peptide having the desired agonist or antagonist activity.
92. A method of assaying a peptide library for agonist or antagonist activity against a non-yeast receptor which comprises providing a yeast culture comprising a plurality of yeast cells, which yeast cells expresses a heterologous G-protein coupled receptor, a G-protein capable of transducing a signal from said receptor to genes in the pheromone signal pathway of said cell, and a heterologous peptide, where, if said peptide is an agonist or antagonist for said receptor, it will stimulate or inhibit, respectively, said pheromone signal pathway, and where said stimulation or inhibition is a screenable or selectable event, which cells each functionally express said receptor and a peptide of said library, said culture collectively expressing the entire peptide library, and determining whether the pheromone signal pathway is activated or inhibited by said peptides in each of the cells of said culture.
93. A method of assaying a peptide for agonist or antagonist activity against a non-yeast receptor which comprises provided yeast cells comprising a plurality of yeast cells, which yeast cells expresses a heterologous G-protein coupled receptor, a G-protein capable of transducing a signal from said receptor to genes in the pheromone signal pathway of said cell, and a heterologous peptide, where, if said peptide is an agonist or antagonist for said receptor, it will stimulate or inhibit, respectively, said pheromone signal pathway, and where said stimulation or inhibition is a screenable or selectable event, which cells functionally express said receptor, and said peptide, and determining whether the pheromone signal pathway is activated or inhibited by said peptide.
94. The method of claim 93 in which the cells comprise a pheromone-responsive selectable marker, and cells are selected for expression of a peptide having the desired agonist or antagonist activity.
95. The method of claim 94 in which the cells comprise a pheromone-responsive screenable marker, and cells are screened for expression of a peptide having the desired agonist or antagonist activity.